CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

#513

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

SUCCESSOR TO THE
TOBACCO INDUSTRY RESEARCH COMMITTEE
633 THIRD AVENUE
NEW YORK, N. Y. 10017

COMMITTEE:
Dr. Cattell, Chm.
Dr. Bing
Dr. Jacobson

Application For Research Grant

Date: October 22, 1965

1. Name of Investigator: HYMAN ENGELBERG, M.D.

2. Title: Attending Physician
Cedars of Lebanon Hospital

3. Institution & Address: Cedars-Sinai Medical Center
Cedars of Lebanon Hospital Division
4833 Fountain Avenue
Los Angeles, California

4. Project or Subject: Smoking and the Thrombosis of Human Blood
Mechanism and Prevention

5. Detailed Plan of Procedure (Use additional pages if more space is required.)

This research is based upon the use of human blood and the Chandler technique which produces a true platelet-head thrombus in vitro rather than a clot. This distinction is an important one (Poole, J.C.F. and French, J.E., J. Atherosclerosis Research 1:251, 1961) since factors involved in clotting may or may not have the same relevance to thrombosis. The proposed research is also based upon the results of a pilot study I have completed in 60 subjects which indicates that there is a statistically significant increased thrombotic tendency, demonstrable in vitro, shortly after smoking. (J.A.M.A. 193:1033, 1965-Sept. 20) (Reprint enclosed).

The mechanisms underlying the markedly increased incidence of myocardial infarction in cigarette smokers have been the subject of much investigation. Nicotine releases epinephrine with a variety of resultant cardiovascular effects which have not been definitely related to the production of atherosclerosis or thrombosis (Blackburn, H., Brozek, J., Taylor, H.L. and Keys, A.: Ann. N.Y. Acad. Sc. 90:277-289, 1960). In a pilot study of 60 smokers (abstract enclosed) I have found that the thrombosis time after smoking was shortened in 34 individuals. The change was highly significant being over 6 times the standard deviation of the method (0.45 minutes as determined by 10 duplicate tests). The effect of smoking on the clotting time was much less than the effect upon the thrombosis time. These preliminary results indicate that there is an accelerated thrombotic tendency soon after smoking in many cigarette smokers. In the presence of coronary atherosclerosis this

1005101167

Source: https://www.industrydocuments.ucsf.edu/docs/jmwn0000

may well be a major additional factor precipitating an acute coronary thrombosis. Heretofore, discussions of smoking in relation to heart disease have involved the effects of smoking on the work of the heart or on coronary flow with little or no mention of coagulation or thrombotic factors (Symposium on the Cardiovascular Effects of Nicotine and Smoking, Ann. N.Y. Acad. Sc. 90:5-344, 1960, and Roth, G.M. & Schick, R. M.. Effect of Smoking on the Cardiovascular System of Man, Circulation 17:443-459, 1958).

In 1958 a relatively simple method was developed for the in vitro production of thrombi using recalcified citrated whole blood (Chandler, A. B. Lab Investigation 7:110, 1958). Essentially the method involves placing recalcified blood in a plastic tube which is then formed into a closed loop and rotated at a speed approximating that of flowing blood in man. The end-point of thrombus formation is the time when the angular position of the head of the column of blood has shifted at least 4^{o} of arc from its original position. Subsequent investigators corroborated the fact that a thrombus with a platelet head was produced by this technique, and studied the effect of saturated and unsaturated fatty acids upon the thrombus formation time (Poole, J.C.F., Quart. J. Exp. Physiol. 44:377, 1959, Connor, W.E. and Poole, J.C.F., ibid 46:1, 1961, Connor, W.E., J. Clin. Investigation 41:1199, 1962).

The Chandler loop apparatus, as modified by Poole, will be used. I have had one of these instruments constructed, at my own expense, with 2 rotating heads so that determinations can be made in duplicate simultaneously. We have performed duplicate tests on 20 blood samples. The method is highly reproducible with a standard deviation of 0.45 minutes. We have compared the results on blood aliquots with silicone technique and with plastic syringes and pipettes, and no difference was found. We therefore propose to use plastic syringes and pipettes.

The smoking tests are done as follows: Patients are seen before breakfast and before smoking. Blood is drawn prior to smoking, directly after smoking and 20 and 60 minutes later. The thrombus formation time tests are run directly after the blood sample is obtained. Determinations of free fatty acids are subsequently made on serum aliquots and of triglycerides in some experiments. (The methods for the lipid determinations have been in use in my research laboratory for years. Free fatty acids will be determined using Dole's method, and triglycerides by the method of Van Handel and Zilversmit).

Although the findings in the first 60 subjects after smoking were statistically significant it is desirable that they be continued and extended. This will afford observations on all types of cigarettes and filters, and also on the effect of cigar and pipe smoking on thrombus formation times. In All further studies of cigarette smoking only one cigarette will be smoked in a normal manner. The results reported in my preliminary communication (J.A.M.A.-Sept. 20, 1965) were obtained after smoking two cigarettes. Larson et al (Tobacco. Experimental and Clinical Studies, Williams and Wilkins Co., Baltimore, 1961) have pointed out that in order to study the effects of smoking, ordinary and not forced smoking

1005101168

Source: https://www.industrydocuments.ucsf.edu/tobacco/

should be used. It is also planned to do repeat tests of the effect of smoking in the same individuals (at least 50) on different days in order to determine the consistency of the response. This is most important for several reasons: (1) It is necessary for the evaluation of drugs that may prevent the thrombotic effect of smoking and the determination of statistically significant results. (2) It is possible that determination of the thrombosing tendency of blood after smoking may lead to a standardized and better test procedure to detect those individuals more or less prone than others to the cardiovascular effects of smoking. It is also necessary to follow thrombus formation times after smoking for 1-4 hours in order to determine how long the effect of smoking persists.

The effect of intravenous or sublingual nicotine, and of I.V. epinephrine and norepinephrine, will be studied on hospitalized clinic patients at the Cedars of Lebanon Hospital. All studies will be in the postabsorptive state. The experimental design is as follows: An intravenous infusion of physiological saline will be started and several blood samples drawn over a half hour period to obtain control observations of fluctuations in the thrombus formation time and free fatty acids. Nicotine bitartrate will then be added to the infusion (2 mg. in a 10 minute period, to approximate the amount absorbed when 1 cigarette is smoked) and blood samples drawn after 5 minutes, at the end of the nicotine infusion, and 30 and 60 minutes later. In those patients in whom nicotine accelerates the thrombosis time it is planned to repeat the procedure another day, after phentolamine (Regitine) is given to see whether this epinephrine blockading agent interferes with the nicotine effect. Pulse rates and blood pressures will be recorded throughout. The use of nicotine I.V. with an initial period of normal saline infusion affords a better controlled study than can be done with smoking. A similar approach will be followed using intravenous epinephrine and norepinephrine. If epinephrine affects the thrombus formation time the studies will be repeated in the same individual ½ hour after the oral administration of 1 gram of nicotinic acid in order to evaluate whether blocking the free fatty acid release after epinephrine also blocks the effect on thrombosis.

All data obtained will be analyzed by the usual statistical tests for significance. In several experiments we have already found that epinephrine accelerates the thrombus formation time but more studies are needed.

The probable mechanism of the smoking effect on thrombosis is by way of the nicotine-induced release of catecholamines and the effect of the latter in enhancing platelet adhesiveness and platelet aggregation (J. R. O'Brien, Nature 200:763, 1963; J. L. Ambrus and I. B. Mink, Clin. Pharmacol. and Ther. 5:428, 1964; J. F. Mustard and E. A. Murphy, Brit. Med. J. 1:846, 1963). This indicates the study of drugs which either decrease catecholamine stores in the body (reserpine), or are adrenergic blockers of various types (propranolol mecamylamide, M. J. 1999, hexamethonium, bretylium, prometholol.) These drugs may prevent or diminish the effect of smoking on thrombus formation. The plan of evaluating these drugs would be to administer them at the usual clinical doses (several weeks for reserpine, several days for the adrenergic blocking agents) to subjects who had shown an accelerated thrombotic tendency after smoking and retest the effect of smoking after taking the drug. The drug would then be stopped and a second control

Source: https://www.industrydocuments.ucsf.edu/docs/jkmh0000

smoking test taken after several weeks. It has been reported that prothrombin depressing drugs delay thrombus formation as studied in the Chandler rotating apparatus. The effect of smoking on thrombus formation times will therefore be tested in a group of patients who are taking oral anticoagulant drugs for coronary heart disease.

Mediation of the thrombosis-accelerating action of smoking via catecholamines suggests that stress and smoking may have a final common pathway in their relationship to myocardial infarction. In fact it is possible that when smoking relaxes tense individuals there may be a decrease in catecholamine release and catecholamine effects. Studies are therefore indicated of the relationship of tension and stress to thrombus formation. This is best done in non-smokers. Although there is some disagreement, it is probable that the measurement of urinary metanephrine and normetanephrine afford the best estimation of sympathetic nervous and adrenomedullary activities (U.S. von Euler, Clin. Pharmacol 5:398, 1964 and R. J. Wurtman, New Eng. J. Med. 273: 637, 1965). In these experiments blood would be drawn before breakfast and the morning urine sample analyzed for metanephrine and normetanephrine. The methods used by Westfall (T. C. Westfall, Effect of Nicotine and Nicotine Analogues on Tissue and Urinary Catecholamines in the Rat, Acta Physiol. Scand. 63: 77, 1965), will be followed.

We have observed that slightly less than half the cigarette smokers tested thus far (J.A.M.A., Sept. 20, 1965) did not have a shortened thrombus formation time after smoking. It would be important to know whether these individuals had a smaller catecholamine release after smoking than those subjects whose thrombus times did shorten on smoking. For this study urinary metanephrine and normetanephrine would be determined on the urine sample obtained at the end of the smoking test (usually one-half hour after smoking), the bladder having been emptied before smoking and a glass of water drunk at that time to guarantee adequate urinary output. The amine analysis would also be done on the urine sample obtained before the smoking procedure.

All data obtained will be statistically analyzed with the usual tests for significance. A full-time statistician is now available at the Cedars of Lebanon Hospital to help in this area.

Finally, an increase in platelet stickiness in half the subjects after smoking two cigarettes has been reported (Ashby et al, Lancet, July 24, 1965, Pg. 158). This is in accord with my published results. However the relation of platelet stickiness to glass to the thrombotic tendency of blood has never been proven. This is only an assumption. For this reason studies using the Chandler loop are preferable, since a true thrombus is produced in a plastic tube.

1005101170

Source: https://www.industrydocuments.ucsf.edu/docs/...

6. Budget Plan:

a.	Salaries*	20, 588
b.	Expendable Supplies	1, 800
c.	Other Expenses	1, 200
d.	Permanent Equipment	1, 265
e.	Overhead (15% of a, b, c)	3, 538
	Total	$28, 391

*3 Technicians' salaries, including 9% fringe benefits.

7. Anticipated Duration of Work:

Three years.

8. Facilities and Staff Available:

My fully equipped biochemical research laboratory in the research building of the Cedars of Lebanon Hospital. I have been doing studies of fat transport for 14 years (see attached bibliography). There is adequate work space for 6 technicians but at present only 2 are employed. The lipid studies are supported by the U. S. P. H. S. Several residents at the hospital are available to work with me directly on the wards if funds are granted. Two additional machines for thrombus formation time determinations are now being built at my expense by the research building machine shop.

9. Additional Requirements:

The $1,265 under permanent equipment is for a Turner fluorometer.

Budget for second year is $28,310, and for the third year is $29,553.

(To the second and third years' budget a 5% increase in salary has been calculated for the three technicians, in accordance with institution policy).

10. Additional Information (Including relation of work to other projects and other sources of support):

This work has no relation to my other projects. I have no other support for this project on smoking and thrombosis.

100510171

Signature Kayman Engelberg M.D.
Director of Project

Arthur E. Bell
Business Officer of the Institution

Source: https://www.industrydocuments.ucsf.edu/docs/jnfw0000

BIBLOIGRAPHY

Hyman Engelberg, M.D.

1. Essential Hypertension. A Comparison of the Hypertensive and Non-hypertensive Phases Following Coronary Thrombosis. Gross, H. and Engelberg, H. Am. J. Med. Sci., 199:620, May 1940.

2. Oil Aspiration (Lipoid) Pneumonia in Adults. A clinicopathologic study of forty-seven cases. Freiman, D. G., Engelberg, H. and Merrit, W. H. Arch. Int. Med. 66:11, July 1940.

3. Comparative Pressor Effects of Paredrine and Paredrinol. Nathanson, M.H. and Engelberg, H. Proc. Soc. Exp. Biol. and Med. 51:239, 1942.

4. Effect of Paredrine on Blood Specific Gravity and Blood Volume. Engelberg, H. and Nathanson, M. H. Ibid, 51:242, 1942.

5. The Cardiovascular Effects of Paredrine. Nathanson, M. H., Engelberg, H. and Hersh, J. Am. Heart J. 24:153, August 1942.

6. Intramuscular Pressure During Postoperative Depression. Gunther, L., Engelberg, H. and Strauss, L. Am. J. Med. Sci. 204:266, August, 1942.

7. Intramuscular Pressure. The Venopressor Mechanism in Shock-like Conditions and the Effects of Various Drugs. Gunther, L., Engelberg, H. and Strauss, L. Ibid. 204:271, August 1942.

8. Intramuscular Pressure. The Action of Various Drugs on Patients with Normal Intramuscular and Venous Pressure. Gunther, L., Strauss, L., Henstell, H. H. and Engelberg, H. Ibid. 204:387, September 1942.

9. Intramuscular Pressure. The Venopressor Mechanism During the Course of Surgical Procedures. Gunther, L., Henstell, H. H., Strauss, L. and Engelberg, H. Ibid.204:391, September 1942.

10. Xanthomatosis. A Cause of Coronary Artery Disease in Young Adults. Engelberg, H. and Newman, B.A. J.A.M.A. 122:1167, August 1943.

11. Effect of Estrogens of Serum Lipids and Low Density Lipoproteins in Men and Women. Glass, S. J., Engelberg, H., Marcus, R. and Gofman, J. Proc. Soc. Exp. Biol. and Med. 80:264, 1952.

12. Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis. Engelberg, H., Gofman, J. and Jones, H. Metabolism 1:300, July 1952.

13. Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis. Engelberg, H., Gofman, J. and Jones, H. Diabetes 1:425, November 1952.

14. Lack of Effect of Administered Estrogen on the Serum Lipids and Lipoproteins of Male and Female Patients. Glass, S., Engelberg, H., Marcus, R., Jones, H. B. and Cofman, J. Metabolism 2:133, March 1953.

15. Heparin Therapy of Severe Coronary Atherosclerosis, with Observations of its Effect on Angina Pectoris, the Two-step Electrocardiograms and the Ballistocardiogram Engelberg, H. Am. J. Med. Sc. 224:487, November 1952.

1005101172

Source: https://www.industrydocuments.ucsf.edu/docs/[illegible]

16. Heparin in the Treatment of Advanced Peripheral Atherosclerosis. A Preliminary Report. Engelberg, H. and Massell, T. B. Am. J. Med. Sci. 225:14, January 1953.

17. Plasma Heparin Levels. I. A. Method for Determination of Plasma Heparin Based on Its Anticoagulant Activity. Freeman, L., Engelberg, H. and Dudley, A. Am. J. Clin. Path. 24:5, May 1954.

18. Relative Merits of Lipoproteins and Cholesterol Determinations in Atherosclerosis. Engelberg, H. J. Am Geriatrics Soc. 2:3, March 1954.

19. Prolonged Anticoagulant Therapy with Subcutaneously Administered Concentrated Aqueous Heparin. Engelberg, H. Surgery 36:4, October 1954.

20. Correlation of Plasma Heparin Levels with Serum Lipoproteins. Engelberg, H. Acta Medica Scand., CLI, Fasc. II, 1955.

21. Human Endogenous Lipemia Clearing Factor. Engelberg, H. Am. J. Physiol. 181:2, May 1955.

22. Influence of Physiologic Doses of Sex Steroid Hormones on Serum Lipids and Lipoproteins in Humans. Engelberg, H. and Glass, S. Metabolism 4:4, July 1955.

23. An Improved Method for the Determination of Plasma Heparin. Engelberg, H., Dudley, A. and Freeman, L. J. of Lab. and Clin. Med. 46:4, October 1955.

24. Studies of Forearm Arterio-Venous Oxygen Differences in Atherosclerotic Patients Before and After Heparin. Engelberg, H. and Kuhn, R. Angiology 7:1, February 1956.

25. A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis. Engelberg, H., Kuhn, R. and Steinman, M. Circulation 13:489, April 1956.

26. The Prophylactic Management of Coronary Atherosclerosis. Engelberg, H. Geriatrics 11:243, June 1956.

27. Human Endogenous Lipemia Clearing Activity. Studies of Lipolysis and Effects of Inhibitors. Engelberg, H. J. Biol. Chem. 222:601, October, 1956.

28. Simplified Herparin Therapy of Impending and Acute Myocardial Infarction. Engelberg, H. Ann. Int. Med. 44:466, March 1956.

29. Human Endogenous Plasma Lipemia Clearing and Lipolytic Activity After Tricalcium Phosphate Adsorption. Engelberg, H. Proc. Soc. Exp. Biol. and Med. 95:394, 1957.

30. Recent Advances in the Etiology, Prevention and Therapy of Atherosclerosis, Engelberg, H. J. Applied Nutrition Vol. 10, 1957 Winter Number.

31. Studies of Circulating Human Endogenous Lipoprotein Lipase (Heparin Lipemia Clearing Factor), Engelberg, H. 3rd Internation Conference on Biochemical Problems of Lipids, "The Blood Lipids and the Clearing Factor". July 1956, Brussels, Belgium.

10051011173

Source: https://www.industrydocuments.ucsf.edu/docs/jmcf0000

32. In Vitro Studies of Human Plasma Lipolytic Activity Before and After Oral Fat Intake. Engelberg, H. J. Applied Physiol. 11:2, 155, September 1957.

33. Studies of Serum Cholesterol and Low Density Lipoprotein Levels Previously Lowered by a Reduced Fat Intake After the Addition of Corn Oil to the Diet. Engelberg, H. J. of Chronic Diseases, 6:3, 229, September 1957.

34. Effect of Pancreatic Lipase and Bile Plus Lipase on Serum Cholesterol and Lipoproteins. Engelberg, H., Steinman, M. and Kuhn, R. Geriatrics 12:700, December 1957.

35. Plasma Heparin Levels in Man Following Intravenous Fat Emulsions. Engelberg, H. Proc. Soc. Exp. Biol. and Med. 97:2, 304, February 1958.

36. DIAGNOSIS OF ATHEROSCLEROSIS: Correlation Between Clinical Diagnosis of Serum Cholesterol and Low-Density Lipoproteins and Resting and Exercise Electrocardiograms. Engelberg, H. Am. J. Cardiology 1:3, 315, March 1958.

37. In Vitro Studies of the Lipolysis of Postalimentary Lipemia in Man. Engelberg, H. Metabolism 7:2, 172 March 1958

38. Anticoagulant Therapy in Acute Myocardial Infarction. Engelberg, H. General Practice, 21:4, p. 11, April 1958.

39. Human Endogenous Plasma Lipemia Clearing Activity After I.V. Fat Emulsions (Lipomul). Engelberg, H. J. Applied Physiology 12:2, 292, March 1958.

40. Quantitative Studies of Triglyceride Lipolysis after Heparin Administration. Engelberg, H., Circulation Research, 6:3, 266-270, May 1958.

41. Effect of Safflower Oil on Serum Cholesterol and Lipoproteins in Patients on a Low-Fat Diet. Engelberg, H., Geriatrics, 13:512-516, August 1958.

42. Effect of Heparin Upon the Total Oxygen Consumption of Atherosclerotic Individuals. Engelberg, H. Am. J. Med. Sc., 236:2, 175-182, August 1958.

43. Human Plasma Heparin Levels and Lipemia Clearing Activity after Ingestion of Animal and Vegetable Fat. Engelberg, H., J. Applied Physiol., 13 (2), 296, September, 1958.

44. Studies Indicating Inactivation of Post-Heparin & Endogenous Human Plasma Lipoprotein Lipase During Triglyceride Lipolysis. Engelberg, H. Proc. Soc. Exp. Biol. & Med. 99:489-493, 1958.

1005101174

45. Human Endogenous Plasma Lipemia Clearing Activity. Observations in 482 Individuals. Engelberg, H. J. App. Physiol. 13:3, 375, Nov. 1958.

46. Correlation Between Serum Lipids & Resting & Exercise Ballistocardiograms. Engelberg, H. Am. J. Cardiology 3:2, 242-246, February 1959.

47. Buccal & Sublingual Administration of Heparin Potassium (Clarin). Engelberg, H. J.A.M.A., 169:1322-1325, March 21, 1959.

48. Effect of Epinephrine Upon Plasma Optical Density, Unesterified Fatty Acids, Lipemia Clearing and Heparin Levels. Engelberg, H. Proc. Soc. Exp. Biol. and Med. 100:492, March 1959.

Source: https://www.industrydocuments.ucsf.edu/docs/jnwn0000

49. Studies of Fat Lipolysis by Post-Heparin Human Plasma Lipoprotein Lipase and by Human Pancreatic Lipase. Engelberg, Hyman. Circulation, v19:884,1959.

50. Lack of Effect of Disodium Calcium EDTA on Human Serum Cholesterol and Low-Density Lipoproteins (24957). Engelberg, Hyman. Proc. of Soc. for Exp. Biol. and Med., v 101:39-400, 1959.

51. Short Term Studies of the Effect of Heparin upon Cholesterol Excretion in Man. Proc. Soc. for Exp. Biol. & Med., v 102:365, Nov. 1959.

52. Advantages of Heparin in the Therapy of Acute Myocardial Infarction. California and Western Medicine, v 91:327, December 1959.

53. Heparin Lipemia Clearing Reaction and Fat Transport in Man. American Journal of Clinical Nutrition, v 8:21, 1960.

54. Liver Function in Humans with Elevated Levels of Serum Cholesterol and/or Low Density Lipoproteins. Circulation, v 22:232, August 1960.

55. Dietary Lipemia and the Clearing Factor. Illinois Medical Journal v 117, No. 6, June 1960.

56. Heparin Versus Heparin-Bishydroxycoumarin Anticoagulant Therapy. Comparison in Patients with Acute Complicated Myocardial Infaction, J.A.M.A. v 174: 1157, October, 1960. Griffith, George C., Zinn, W.J., Engelberg, H., Dooley, J.V. and Anderson, Richard.

57. Plasma Heparin Levels. Correlation with Serum Cholesterol and Low Density Lipoproteins. Circulation v 23:573, April 1961.

58. Plasma Heparin Levels in Normal Man. Circulation, v23:578, April 1961.

59. Absence of Lipemia Clearing Factor Lipase in Human Adipose Tissue. J. of Lipid Research. v2:169, April 1961.

60. The Effect of Heparin Upon the Excretion of Cholesterol End-Products in Man. Metabolism, v10: 439, 1961.

61. Heparin Lipemia Clearing Reaction and Fat Transport. Engelberg, Hyman. Proceedings of the Seventh Microcirculatory Conference. "Intravascular Phenomena", p. 17, May 1959.

62. Idopathic Hyperlipemia. Med. Bull. of the Childrens Hospital, L.A. v8:109, 1961.

63. Anticoagulants in Acute Myocardial Infarction. Lancet, Letters to the Editor, p. 103-104, Jan. 13, 1962.

64. Effect of Sodium D-thyroxine on Serum Cholesterol and Low-Density Lipoproteins in Man. Geriatrics v17:711, 1962.

65. Mechanism Underlying Hypercholesterolemia and Hypertriglyceridemia. Diseases of the Chest. v 42:119, 1962.

1005101175

Source: https://www.industrydocuments.ucsf.edu/docs/jmvh0000

66. Effects of Sulfated Mucopolysaccharides and of Endogenous Plasma Heparin(s) on Thromboplastin Generation (27344). Proc. of Soc. for Exp. Biol. & Med. v 109:814-817, 1962.

67. Effects of Triparanol on Serum Low-Density Lipoproteins and Cholesterol. Geriatrics, v 17: 528-531, 1962.

68. Lipid Metabolic Studies in Patients with Essential Hypertriglyceridemia. Metabolism, v 11: 1250, 1962.

69. Studies of Human Serum and Plasma Inhibition of Lipase Activity of Post-Heparin Clearing Factor. Am. J. of Clinical Pathology, v 18: No. 4: 367-370, Oct.1962.

70. HEPARIN - Metabolism, Physiology and Clinical Application. Charles C. Thomas-1963.

71. Incidence of Endogenous Lipoprotein Lipase Activity in Human Plasma (29267). Proc. of Soc. for Exp. Biol. & Med., v 116, No. 2: 422-425, 1964.

72. Heparin and the Removal of Triglyceride from the Bloodstream. Am. J. of Cardiology. 14:8-17, 1964.

73. The Effect of a Heparin Antagonist on Fasting Serum Triglycerides in Man. Journal of Atherosclerosis Research. To be published. 1965.

74. The Effect of Cigarette Smoking upon the Thrombosis of Human Blood in Vitro. J. A. M. A. 193:117-119, September 20, 1965.

100510176

Source: https://www.industrydocuments.ucsf.edu/docs/[illegible]